ANALYSIS OF 50 CASES OF DEMYELINATING DISEASES OF CENTRAL NERVOUS SYSTEM

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COIMBATORE

CERTIFICATE

This is to certify that the Dissertation entitled **"Analysis of 50 cases of demyelinating diseases of central nervous system"** herewith submitted by **Dr.SHANIJA.P,** Post Graduate in General Medicine , Coimbatore Medical College to the **Tamilnadu Dr**. ***M.G.R***. **Medical University** is a record of a bonafide research work carried out by her under my guidance and supervision from APRIL 2007 to SEP 2008.

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DEAN

DECLARATION

I solemnly declare that the Dissertation titled **" Analysis of 50 cases of demyelinating diseases of central nervous system "**, was done by me at Coimbatore Medical College & Hospital during the period from APRIL 2007 to SEP 2008 under the guidance and supervision of **Prof. Dr.K.UMAKANTHAN M.D.,** and **Prof. Dr.P.JAMBULINGAM M.D.,**

This dissertation is submitted to the Tamilnadu Dr. ***M.G.R***. Medical University towards the partial fulfillment of the requirement for the award of M.D. Degree (Branch *I*) in General Medicine.

Place : Coimbatore **DR. SHANIJA.P**

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INTRODUCTION

Demyelinating disorders of CNS are characterized by inflammation and selective destruction of central nervous system (CNS) myelin. The peripheral nervous system (PNS) is spared and most patients have no evidence of an associated systemic illness. Inflammatory demyelinating diseases of the central nervous system occur through out the world and are the foremost cause of the nontraumatic neurological disability in young adults.

Multiple sclerosis is the most common of these disorders. . This enigmatic, relapsing, and often eventually progressive disorder of the white matter of the central nervous system continues to challenge investigators trying to understand the pathogenesis of the disease and prevent its progression.(1)

Multiple sclerosis (MS) is characterized by a triad of inflammation, demyelination, and gliosis (scarring); the course can be relapsing-remitting or progressive. Lesions of MS typically occur at different times and in different CNS locations. Multiple sclerosis typically begins in early adulthood and has a variable prognosis. Manifestations of MS vary from a benign illness to a rapidly evolving and incapacitating disease requiring profound lifestyle adjustments. Fifty percent of patients will need help walking within 15 years after the onset of disease.

Advanced magnetic resonance imaging (MRI) and spectroscopy may allow clinicians to follow the pathological progression of the disease and monitor the response to treatment.The visible T2 lesions are diagnostically valuable and may allow earlier

diagnosis of the disease and more accurate prognostication(2). Recent progress has occurred in understanding the cause, the genetic components, and the pathologic process of multiple sclerosis. The short-term clinical and MRI manifestations of disease activity have been reduced by new therapies, although the degree of presumed long-term benefit from these treatments will require further study.

However Multiple Sclerosis represents only one member of a family of CNS idiopathic inflammatory demyelinating diseases which also include acute transverse myelitis, Acute disseminated encephalomyelitis, (ADEM) and Neuromyelitis optica (Devics disease). Although these disorders are all similarly characterized by focal CNS demyelination they vary in their clinical course, prognosis, regional distribution, pathology and pathogenesis.

AIM OF THE STUDY

1.To study the clinical presentation and course of different demyelinating diseases of CNS.

2. To find out the prevalence of primary and secondary demyelinating disease of CNS in adult patients.

3. To correlate the MRI abnormalities and clinical disability in patients.

4. Short term follow up of patients.

REVIEW OF LITERATURE

CLASSIFICATION OF DEMYELINATING DISEASES:

The aetiology of most demyelinating disorders is unknown. In some cases genetical factors are involved; others may follow viral infections such as measles and small pox or vaccination, and demyelination or destruction of nerve fibres and surrounding myelin occurs in a wide variety of disorders involving the nervous system

Demyelination can be regarded as either primary or secondary. The primary form destroys or damages myelin or myelin-forming cells and axons are relatively normal, at least in the early stages. Secondary demyelination, on the other hand, causes damage to neurons or axons, followed by breakdown of myelin.

Current classification depends upon a mixture of clinical and pathological features, including genetics, biochemical and immunological abnormalities. Some metabolic defects influence the formation of myelin rather than damage to myelin once it has been formed. The group of diseases associated with specific metabolic defects influencing the formation of myelin have now been separated under the general term "dysmyelinating disorders or leukodystrophies".

Table : 1

Disorders That Can Cause CNS Demyelination	
Category	**Disorders**
Hereditary disorders	Phenylketonuria and other aminoacidurias Tay-Sachs, Niemann-Pick, and Gaucher's diseases Hurler's syndrome Krabbe's disease and other leukodystrophies Adrenoleukodystrophies Adrenomyeloneuropathy Leber's hereditary optic atrophy and related mitochondrial disorders
Hypoxia and ischemia	Carbon monoxide toxicity and other syndromes of delayed hypoxic cerebral demyelination Progressive subcortical ischemic demyelination
Nutritional deficiencies	Central pontine myelinolysis (may also be caused by Na fluxes) Demyelination of the corpus callosum (Marchiafava-Bignami disease) Vitamin B_{12} deficiency
Direct viral invasion of CNS	Progressive multifocal leukoencephalopathy Subacute sclerosing panencephalitis Tropical spastic paraparesis/HTLV-1–associated myelopathy
Primary demyelinating disorders	Recurrent, progressive disorders (multiple sclerosis and its variants) Monophasic disorders such as optic neuritis, acute transverse myelitis, acute disseminated encephalomyelitis, and acute hemorrhagic leukoencephalitis Neuromyelitis optica

.MULTIPLE SCLEROSIS

More than 100 years has passed since Charcot, Carswell, Cruveilhier, and others described the clinical and pathological characteristics of multiple sclerosis(3). Multiple sclerosis (MS) is characterized by a triad of inflammation, demyelination, and gliosis (scarring); the course can be relapsing-remitting or progressive.

AGE DISTRIBUTION:

Multiple sclerosis is a disease of young adults; the mean age of onset is 29-33 years, but the range of onset is extremely broad from approximately 10-59 years.

SEX DISTRIBUTION:

Women are more likely to develop multiple sclerosis than men, with MS occurring

50% more frequently in women than in men.

GENETIC FACTORS:

The concordance rate of 31 percent among monozygotic twins is approximately six times the rate among dizygotic twins (5 percent)(4). The absolute risk of the disease in a first-degree relative of a patient with multiple sclerosis is less than 5 percent; however, the risk in such relatives is 20 to 40 times the risk in the general population(5). Since 1973, it has been recognized that the presence of the HLA-DR2 allele substantially increases the risk of multiple sclerosis.(6)

PATHOLOGICAL FEATURES AND PATHOGENESIS:

Multiple sclerosis is generally believed to be an immune- mediated disorder that occurs in genetically susceptible people,(7). The pathological hallmark of chronic multiple sclerosis is the demyelinated plaque, which consists of a well-demarcated hypocellular area characterized by the loss of myelin, relative preservation of axons, and the formation of astrocytic scars .

Lesions have a predilection for the optic nerves, periventricular white matter, brain stem, cerebellum, and spinal cord white matter, and they often surround one or several medium-sized vessels. Although the lesions are usually round or oval, they often have finger-like extensions along the path of small or medium-sized blood vessels (Dawson's fingers).

Inflammatory cells are typically perivascular in location, but they may diffusely infiltrate the parenchyma. The inflammatory infiltrate is composed of lymphocytes and macrophages; the latter predominate in active lesions. Identifying myelin-degradation products in macrophages is the most reliable method of identifying active lesions (8).

Furthermore, the lesions of chronic multiple sclerosis reportedly contain substantial numbers of oligodendrocyte precursor cells.(9) Activated CD4+ T cells specific for one or more self antigens are believed to adhere to the luminal surface of endothelial cells in central nervous system venules and migrate into the central nervous system at the time of disruption of the blood–brain barrier. This process is followed by

an amplification of the immune response after the recognition of target antigens on antigen-presenting cells. The existence of T cells that are reactive to several putative self myelin and non-myelin "multiple sclerosis antigens," including myelin basic protein, myelin-associated glycoprotein, myelin oligodendrocyte glycoprotein, proteolipid protein, B-crystallin, phosphodiesterases, and S-100 protein, has been proposed.(10-12).

Additional amplification factors including autoantibodies or cytokines may also be necessary to produce the demyelinated plaque (13) Antibodies against antigens located on the surface of the myelin sheath or oligodendrocyte can cause demyelination directly, possibly through the activation of complement, leading to complement-mediated cytolysis. (14) Antibodies against both myelin oligodendrocyte glycoprotein and myelin basic protein can be found in the brains of patients with multiple sclerosis. (15). Deposits of immunoglobulin and activated complement may be present in multiple sclerosis lesions in which myelin is being degraded. (16)

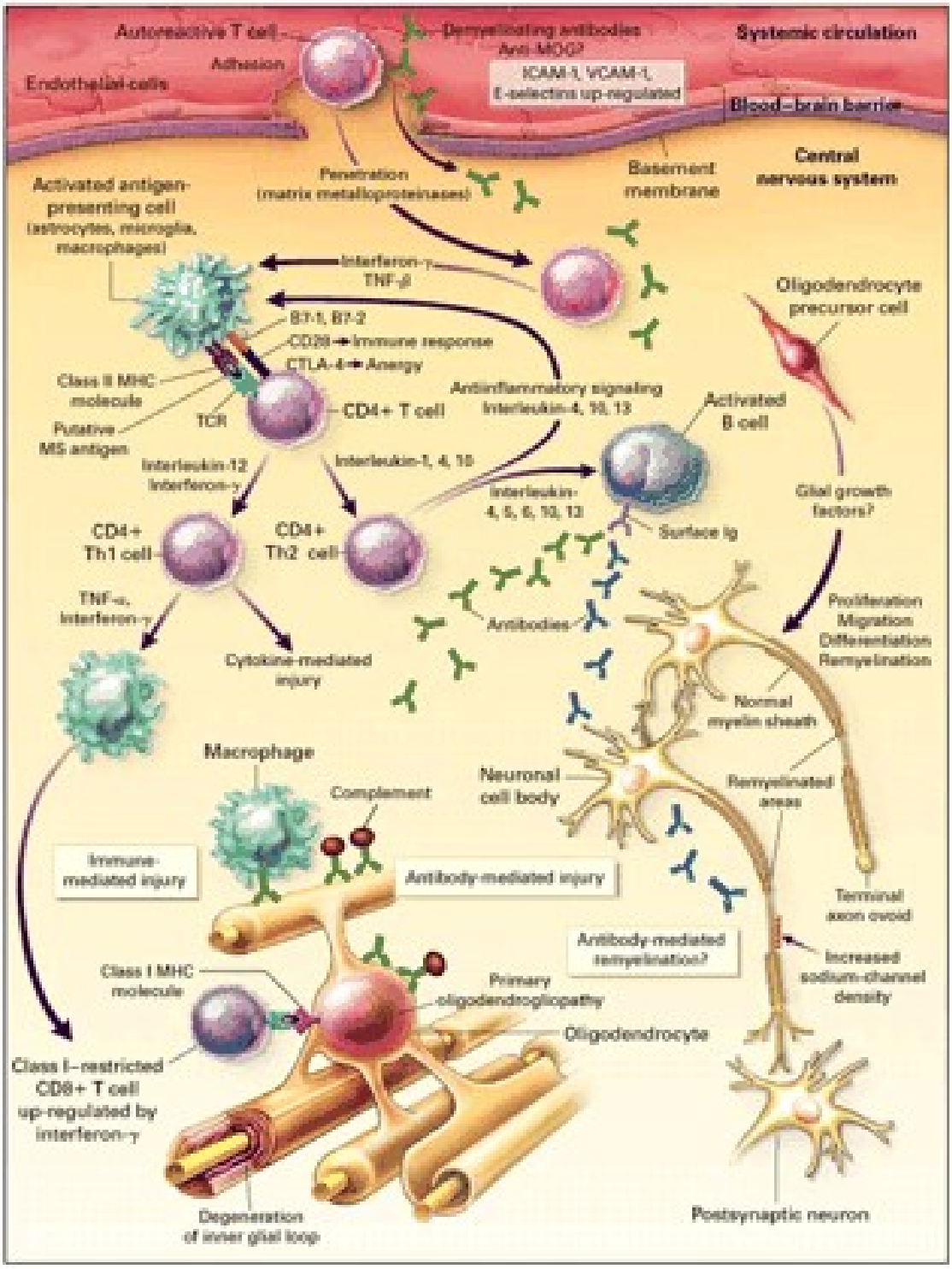
Other factors potentially toxic to oligodendroglial cells include soluble T-cell products (such as perforin), the interaction of Fas antigen with Fas ligand, cytotoxicity mediated by the interaction of CD8+ T cells with class I major- histocompatibility-complex (MHC) antigens on antigen-presenting cells, and persistent viral infection(17).Human herpesvirus type 6 can cause a condition that mimics multiple sclerosis (18). and appears in oligodendrocytes within multiple sclerosis tissue in some patients, but not in control tissue(19).

MRI and spectroscopy may be helpful in characterizing the underlying pathologic

processes in multiple sclerosis(20). Monitoring by means of serial MRI studies with gadolinium enhancement helps to identify agents that may be active against this early inflammatory stage of multiple sclerosis (e.g., corticosteroids, interferons, glatiramer acetate, and certain immunosuppressive agents).(21-25) There is MRI and pathological evidence that the normal-appearing white matter is not normal in patients with multiple sclerosis.(26-28).

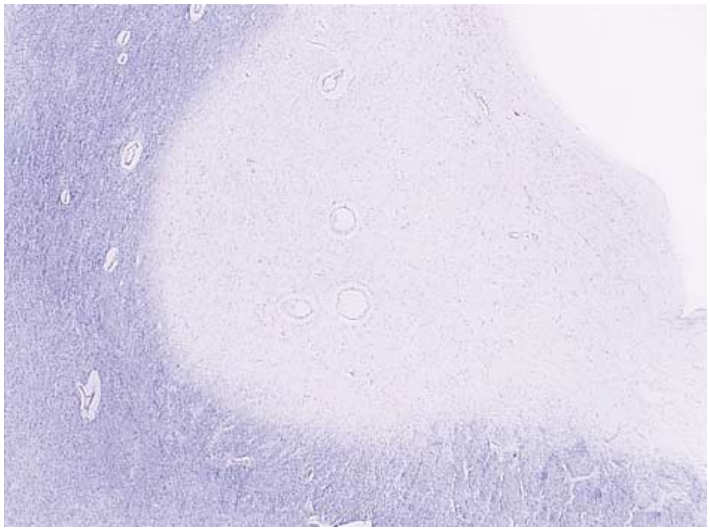
Possible Mechanisms of Injury and Repair in Multiple Sclerosis

Fig : 1

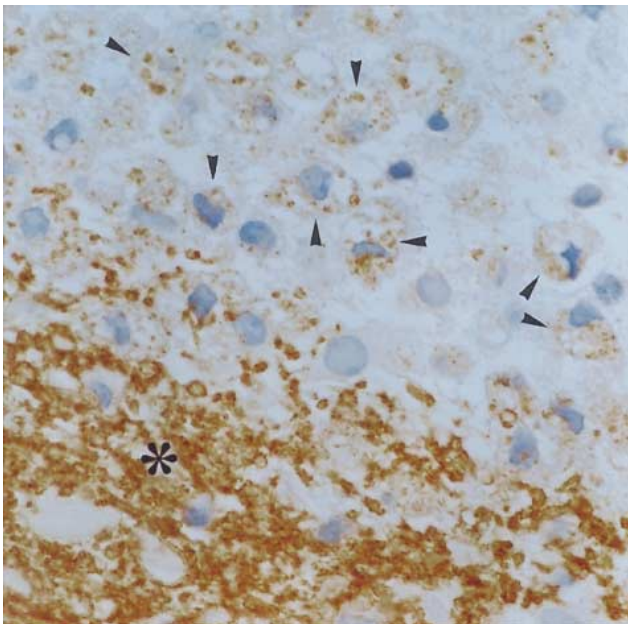


Photomicrographs of a Chronic Multiple Sclerosis Plaque. hypocellular region of myelin loss is evident in the periventricular white matter

Fig : 2



Photomicrographs of an Actively Demyelinating Multiple Sclerosis Lesion at the active edge of a multiple sclerosis plaque (indicated by the asterisk), the products of myelin degradation are present in numerous macrophages (arrowheads). Fig : 3



CLINICAL COURSE AND DIAGNOSIS:

In **relapsing–remitting multiple sclerosis** — the type present in 80 percent of patients — symptoms and signs typically evolve over a period of several days, stabilize, and then often improve, spontaneously or in response to corticosteroids, within weeks.

Relapsing–remitting multiple sclerosis typically begins in the second or third decade of life and has a female predominance of approximately 2:1. Persistent signs of central nervous system dysfunction may develop after a relapse, and the disease may progress between relapses (**secondary progressive multiple sclerosis**). Twenty percent of affected patients have **primary progressive multiple sclerosis**, which is characterized by a gradually progressive clinical course and a similar incidence among men and women.

Relapsing–remitting multiple sclerosis typically starts with sensory disturbances, unilateral optic neuritis, diplopia (internuclear ophthalmoplegia), Lhermitte's sign (trunk and limb paresthesias evoked by neck flexion), limb weakness, clumsiness, gait ataxia, and neurogenic bladder and bowel symptoms. Many patients describe fatigue that is worse in the afternoon and is accompanied by physiologic increases in body temperature. The onset of symptoms post partum and symptomatic worsening with increases in body temperature (Uhthoff's phenomenon) and pseudoexacerbations with fever suggest the diagnosis. Some patients have recurring, brief, stereotypical phenomena (paroxysmal pain or paresthesias, trigeminal neuralgia, episodic clumsiness or dysarthria, and tonic limb posturing) that are highly suggestive of multiple sclerosis. Prominent cortical signs (aphasia, apraxia, recurrent seizures, visual-field loss, and early dementia) and extrapyramidal phenomena (chorea and rigidity) only rarely dominate the clinical picture. Eventually, cognitive impairment, depression, emotional lability, dysarthria, dysphagia, vertigo, progressive quadriparesis and sensory loss, ataxic

tremors, pain, sexual dysfunction, spasticity, and other manifestations of central nervous system dysfunction may become troublesome.

Patients who have primary progressive multiple sclerosis often present with a slowly evolving uppermotor neuron syndrome of the legs (“chronic progressive myelopathy”). Typically, this variant worsens gradually, and quadriparesis, cognitive decline, visual loss, brain-stem syndromes, and cerebellar, bowel, bladder, and sexual dysfunction may develop.

The diagnosis is based on established clinical and, when necessary, laboratory criteria-Mac Donalds criteria(28).

MAC DONALDS CRITERIA : Table : 2

Clinical presentation	**Additional evidence required for diagnosis of MS**
Two or more attacks separated in 'time' (at least 3 months apart) and 'space' (involving different parts of the CNS) with objective clinical evidence of two or more lesions	None
Two or more attacks separated in 'time' and 'space', but with objective clinical evidence for only one lesion	MRI demonstrates dissemination in 'space' (multiple lesions in severaldifferent sites) *or* Two or more MRI-detected lesions consistent with MS *and* oligoclonal bands in CSF *or* Await further clinical attack at different anatomical site
One attack with objective clinical evidence of two or more lesions in different parts of the CNS (i.e. dissemination in 'space')	Dissemination in 'time', demonstrated by serial MRI scans (looking for a new lesion developing at least 3 months after the inital presentation) *or* Await further (second) clinical attack at

	different anatomical site
One attack with clinical evidence of only one lesion (clinically isolated syndrome)	MRI demonstration of dissemination in 'space' and 'time' (as above) *or* Two or more MRI-detected lesions with CSF showing oligoclonal bands *and* dissemination in time, demonstrated by MRI *or* Await further (second) clinical attack at different anatomical site
Insidious neurological progression suggestive of MS	CSF positive for oligoclonal bands *and* Dissemination in 'space' and 'time' on MRI and/or abnormal VER[3] *or* Continued progression for a year

Clinically isolated idiopathic inflammatory demyelinating diseases such as optic neuritis(ON) , ATM, and tumefactive demyelinating lesions have the potential to convert to relapsing -remittig MS(RRMS). currently available disease modifying drugs delay the conversion to definite MS. This delay may be more prominent for patients who present with ATM than for patients who present with ON. Following an acute episode of complete ATM with longitudinal spinal cord lesions , there is 40% chance of devolepment of NMO at one year which can be predicted by the presence of specific antibody marker , NMO Immunoglobulin IgG.

INVESTIGATIONS:

Advances in cerebrospinal fluid analysis and MRI, in particular, have simplified the diagnostic process(29). The relapsing forms are considered clinically definite when neurologic dysfunction becomes “disseminated in space and time .On MRI, findings of multifocal lesions of various ages, especially those involving the periventricular white matter, brain stem, cerebellum, and spinal cord white matter, support the clinical

impression. The presence of gadolinium-enhancing lesions on MRI indicates current sites of presumed inflammatory demyelination (active lesions). When there is diagnostic uncertainty, repeated MRI after several months may provide evidence that the lesions are “disseminated in time.”

Physiologic evidence of subclinical dysfunction of the optic nerves and spinal cord (changes in visual evoked responses and somatosensory evoked potentials) may provide support for the conclusion that there is “dissemination in space.”(30). Therefore, spinal MRI and evoked-potential testing may provide evidence of a second lesion that can confirm the diagnosis. Abnormalities detected by testing of somatosensory evoked potentials and spinal MRI may clarify the diagnosis in patients with optic neuritis alone or isolated brain-stem abnormalities and in those suspected of having unifocal cerebral multiple sclerosis on the basis of MRI. Patients who have a so-called clinically isolated syndrome (e.g., optic neuritis, brain-stem dysfunction, or incomplete transverse myelitis) as their first event have a greater risk of both recurrent events (thereby confirming the diagnosis of clinically definite multiple sclerosis) and disability within a decade if changes are seen in clinically asymptomatic regions on MRI of the brain, three or more T2 weighted lesions in MRI the risk of devoleping MS after 10 years is 70 – 80% (31) The presence of oligoclonal bands in cerebrospinal fluid slightly increases the risk of recurrent disease.(32)

The total volume of T2-weighted signal abnormality (the "burden of disease") shows a significant (albeit weak) correlation with clinical disability, as do measures of

brain atrophy. Approximately one-third of T2-weighted lesions appear as hypointense lesions (black holes) on T1-weighted imaging. Black holes may be a marker of irreversible demyelination and axonal loss, although even this measure depends on the timing of the image acquisition (e.g., most acute Gd-enhancing T2 lesions are T1 dark).

Newer MRI measures such as magnetization transfer ratio (MTR) imaging and proton magnetic resonance spectroscopic imaging (MRSI) may ultimately serve as surrogate markers of clinical disability.

Ten percent of patients do well for more than 20 years and are thus considered to have benign multiple sclerosis. Approximately 70 percent will have secondary progression(33). Frequent relapses in the first two years, a progressive course from the onset, male sex, and early, permanent motor or cerebellar findings are independently, but imperfectly, predictive of a more severe clinical course. Women and patients with predominantly sensory symptoms and optic neuritis have a more favorable prognosis.Suicide remains a risk, even for young patients with mild symptoms(34).

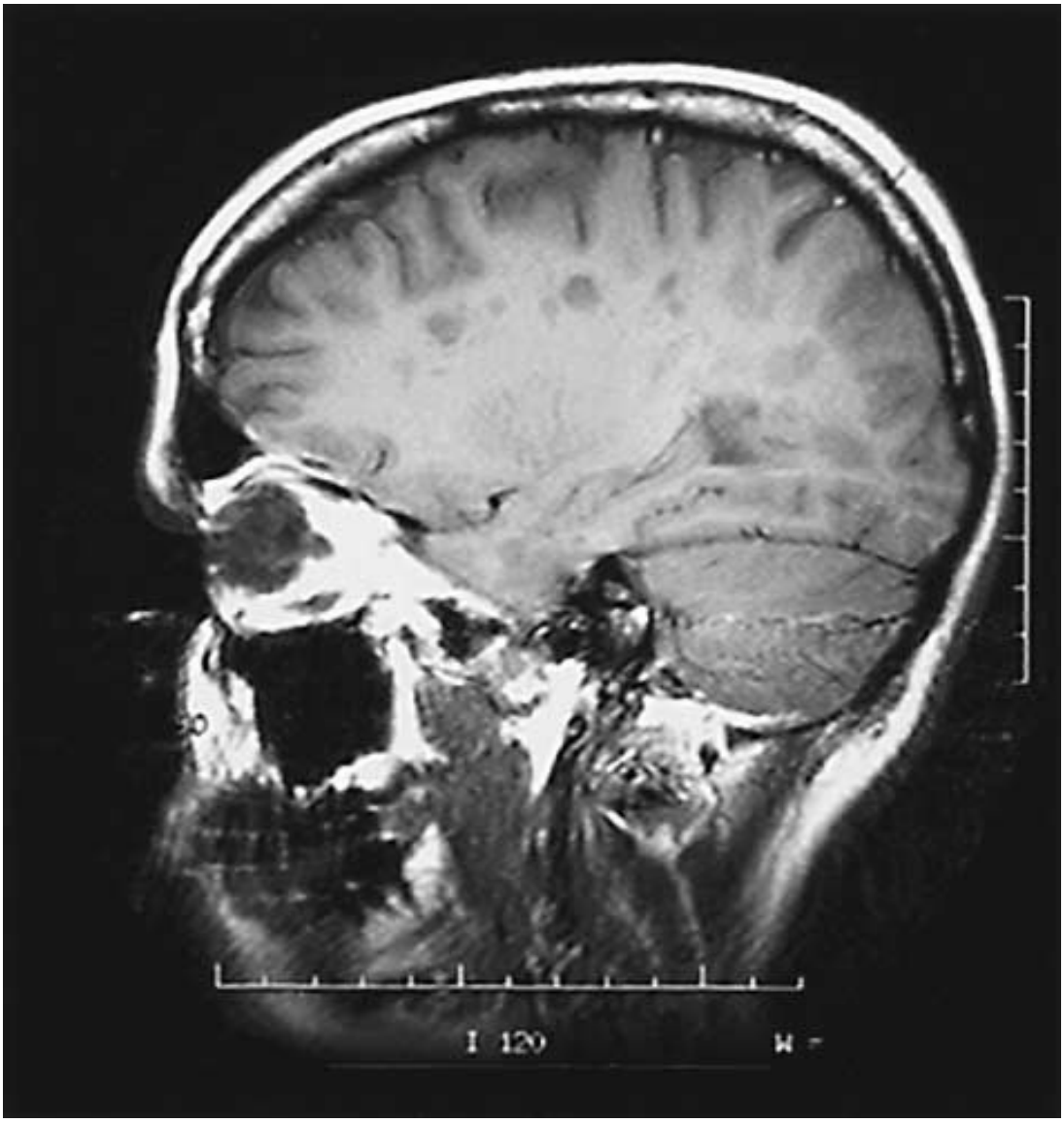
MRI SCANS OF THE BRAIN OF A 25-YEAR-OLD WOMAN WITH RELAPSING– REMITTING MULTIPLE SCLEROSIS. Fig : 4

Axial FLAIR (fluid-attenuated inversion recovery) image shows multiple ovoid and confluent hyperintense lesions in the periventricular white matter

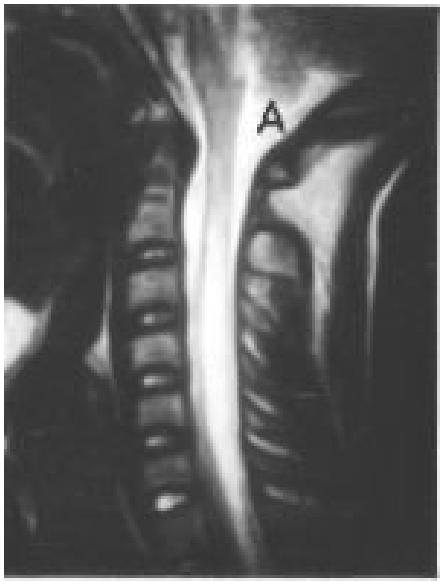
.

After the administration of gadolinium, many of the lesions demonstrate ring or peripheral enhancement, indicating the breakdown of the blood–brain barrier Fig : 5

Parasagittal T-weighted MRI scan shows multiple regions in which the signal is diminished (referred to as “black holes”) in the periventricular white matter and corpus callosum. These regions correspond to the chronic lesions of multiple sclerosis. Fig : 6



MRI of the cervical spine showing hyperintense signal on T2W image, extending over multiple segments. Fig : 7



MRI of dorsal spine (sagittal section) showing hyperintense signal on T2W image

extending over less than 2 vertebralsegments fig:8

CEREBROSPINAL FLUID ANALYSIS :

CSF abnormalities/ found in MS include a mononuclear cell pleocytosis and an increased level of intrathecally synthesized IgG. The total CSF protein is usually normal or slightly elevated. The measurement of oligoclonal banding (OCB) in the CSF also assesses intrathecal production of IgG. OCBs are detected by agarose gel electrophoresis. Two or more OCBs are found in 75–90% of patients with MS. OCBs may be absent at the onset of MS, and in individual patients the number of bands may increase with time.

OLIGOCLONAL BAND:

Multiple sclerosis (MS) - diagnosis aided by the detection of oligoclonal bands (OCB) in the cerebrospinal fluid (CSF).

- More than 95% of patients with multiple sclerosis have OCB (2 or more) in the CSF (intrathecal IgG synthesis).
- There is no correlation between OCB in CSF and demyelinating process.
- OCB can be present even when the CSF IgG level is normal.
- Once an oligoclonal response is established, it can be maintained for the natural life of the patient (except in cases of some CNS infections).
- OCB have been reported in other cases, for example, neurosyphilis, acute bacterial or viral meningitis, progressive multifocal leukoencephalopathy,

subacute sclerosing panencephalitis, progressive rubella panencephalitis, polyneuritis, optic neuritis, trypanosomiasis, and other infectious or autoimmune diseases.

- Isoelectric focusing is most sensitive method for detection of the OCB.

Below are which are likely to be seen. ***The most important pattern of OCB in MS is intrathecal IgG synthesis (blot 2 and 3).***

1. (S -ve, C -ve):

- No evidence of intrathecal IgG synthesis (Normal).

2. (S -ve, C +ve):

- Oligoclonal bands present in CSF only.

- I**ntrathecal IgG synthesis seen in MS**.

3. (S +ve, C +ve):

- Identical pattern of bands in both serum and CSF with- extra bands in CSF.

- I**ntrathecal and systemic IgG synthesis seen in MS**.

4. (S +ve, C +ve):

- Identical pattern of bands in both serum and CSF.

- Systemic IgG synthesis.

5. (S +ve, C +ve):

- Abnormal identical pattern of bands in both serum and CSF

- Usually seen with a monoclonal protein.

- Suggests peripheral IgG synthesis.

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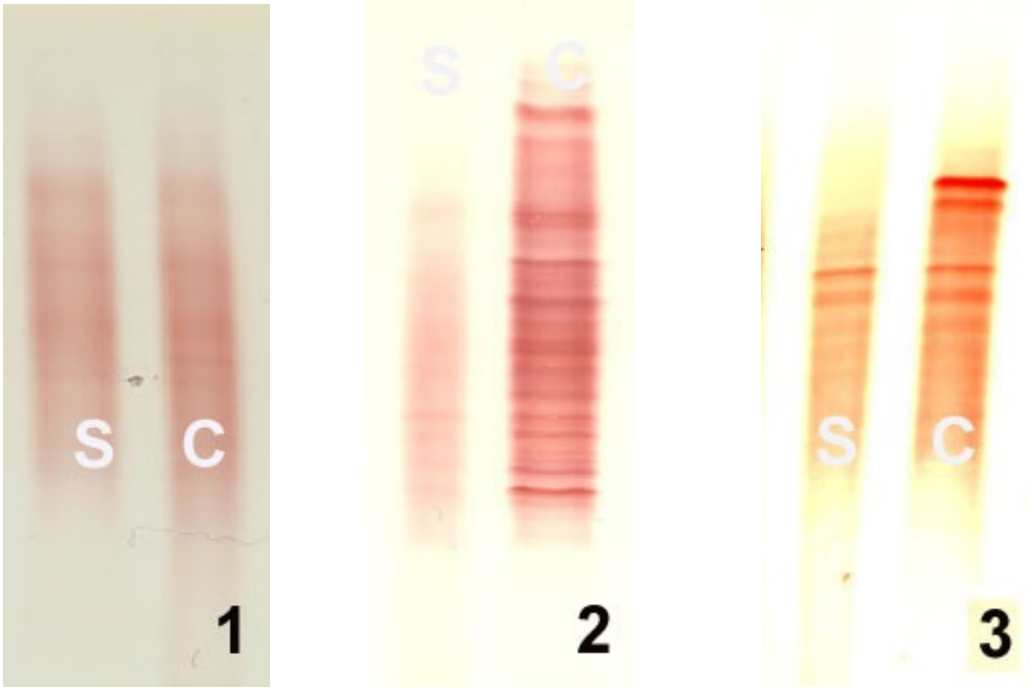


S = Serum, C = CSF, The blot number also represents the anode side. fig : 9A

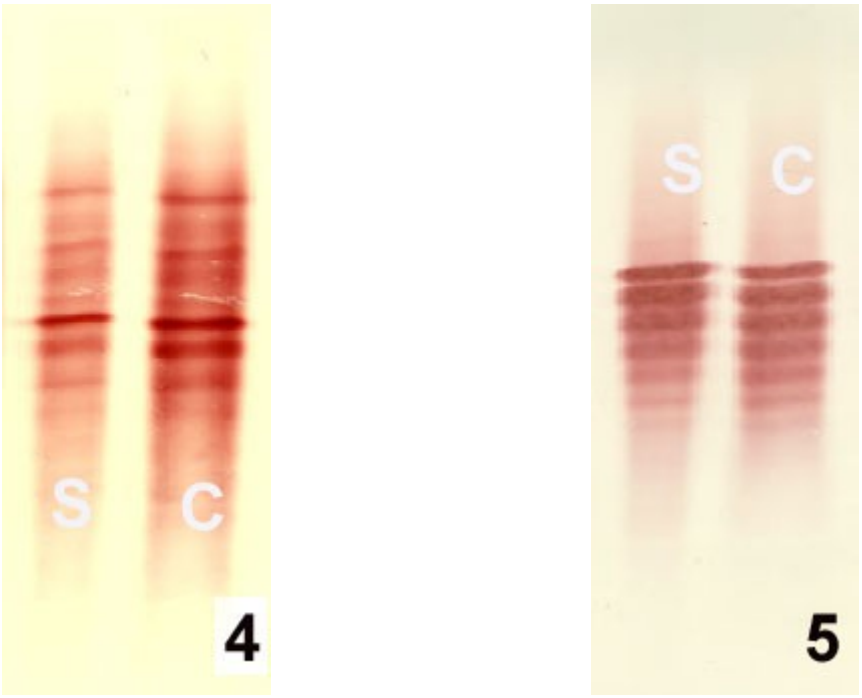


Fig : 9B

DIFFERENTIAL DIAGNOSIS OF MULTIPLE SCLEROSIS Table :3

1. Acute disseminated encephalomyelitis (ADEM)
2. Antiphospholipid antibody syndrome
3. Behçet's disease
4. Cerebral autosomal dominant arteriopathy, subcortical infarcts, and leukoencephalopathy (CADASIL)
5. Congenital leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy)
6. Human immunodeficiency virus (HIV) infection
7. Ischemic optic neuropathy (arteritic and nonarteritic)
8. Lyme disease
9. Mitochondrial encephalopathy with lactic acidosis and stroke (MELAS)
10. Neoplasms (e.g., lymphoma, glioma, meningioma)

11. Sarcoid
12. Sjögren's syndrome
13. Stroke and ischemic cerebrovascular disease
14. Syphilis
15. Systemic lupus erythematosus and related collagen vascular disorders
16. Tropical spastic paraparesis (HTLV I/II infection)
17. Vascular malformations (especially spinal dural AV fistulas)
18. Vasculitis (primary CNS or other)

19. Vitamin B_{12} deficiency

VARIANTS OF MULTIPLE SCLEROSIS:

- Optic neuritis
- Isolated brain-stem syndromes
- Marburg disease
- Neuromyelitis optica
- Schilder's disease
- Balo's disease

TREATMENT:

Therapy for MS can be divided into several categories: (1) treatment of acute attacks as they occur, (2) treatment with disease-modifying agents that reduce the biological activity of MS, and (3) symptomatic therapy

The Kurtzke Expanded Disability Status Score (EDSS) is a useful measure of neurologic impairment in MS . Most patients with EDSS scores <3.5 have RRMS, walk normally, and are generally not disabled; by contrast, patients with EDSS scores >5.5 have progressive MS (SPMS or PPMS), are gait-impaired and, typically, are occupationally disabled. (35)

ACUTE ATTACKS OR INITIAL DEMYELINATING EPISODES :

When patients experience acute deterioration, it is important to consider whether this change reflects new disease activity or a "pseudoexacerbation" resulting from an increase in ambient temperature, fever, or an infection. In such instances, glucocorticoid treatment is inappropriate. Glucocorticoids are used to manage either first attacks or acute exacerbations. They provide short-term clinical benefit by reducing the severity and shortening the duration of attacks .

Glucocorticoid treatment is usually administered as intravenous methylprednisolone, 500–1000 mg/d for 3–5 days, either without a taper or followed by a course of oral prednisone beginning at a dose of 60–80 mg/d and gradually tapered over 2 weeks. Outpatient treatment is usually possible. If intravenous therapy is unavailable or inconvenient, oral glucocorticoids can be substituted.

DISEASE-MODIFYING THERAPIES FOR RELAPSING FORMS OF MS (RRMS, SPMS WITH EXACERBATIONS)

Five agents are approved in the United States: (1) IFN--1a (2) IFN--1b (3) glatiramer acetate, and (4) natalizumab and (5)Mitoxantrone

Interferon beta-1a and interferon beta-1b and glatiramer acetate (36,37) were subsequently found to reduce the frequency of relapse. Interferon beta-1a may delay the progression of disability in patients with minor disability who have a relapsing form of multiple sclerosis.(38,39).

Glatiramer acetate, formerly known as copolymer-1, is a mixture of synthetic polypeptides containing the L-amino acids glutamic acid, alanine, lysine, and tyrosine. Glatiramer acetate may promote the proliferation of Th2 cytokines; compete with myelin basic protein for presentation on MHC class II molecules, thereby inhibiting antigen-specific T-cell activation ; alter the function of macrophages; and induce antigen-specific suppressor T cells.

Interferon beta-1a and interferon beta-1b may induce the formation of neutralizing antibodies, especially during the first 18 months of treatment.

TREATMENT OF COMPLICATIONS :

There are moderately effective treatments for several of the complications of multiple sclerosis. Fatigue may respond to amantadine and to energy-conservation strategies. Depression and sleep disorders may contribute to fatigue and must be recognized and treated appropriately. Paroxysmal events typically respond well to carbamazepine and phenytoin (alone or in combination), acetazolamide, gabapentin, and pergolide. spasticity pain, problems with gait, decubitus ulcers, speech and swallowing disorders, and cognitive andmood disorders are best treated by a multi-disciplinary approach that may involve specialists in physical medicine and rehabilitation. Stretching, a programme of aerobic exercise, and centrally acting muscle relaxants may help patients with mild, symptomatic spasticity The implantation of a pump for the intrathecal administration of baclofen may assist in the management of intractable painful spasticity .Neurogenic bladder and bowel disturbances are amenable to treatment after appropriate investigations have clarified the underlying physiologic mechanisms. Sexual dysfunction and chronic, central pain are common and may respond to appropriate symptom-based treatment strategies. Disabling, high-amplitude, cerebellar tremors rarely respond well to medication but may decrease after continued contralateral thalamic stimulation or ablative thalamotomy.

CHALLENGES IN CONDUCTING CLINICAL TRIALS AND FUTURE DIRECTIONS:

Multiple sclerosis remains a challenging disease to study because the cause is unknown, the pathophysiologic mechanisms are diverse, and the chronic, unpredictable course of the disease makes it difficult to determine whether the favorable effects of short-term treatment will be sustained. Most published trials are small (usually including fewer than 150 patients per study group) and brief (less than three years of follow-up(40). In past several years, trials have used increasingly sophisticated methods to identify promising agents(41-43)

Investigators who favor an infectious cause of multiple sclerosis, such as human herpesvirus type 660 or *C. pneumoniae,*(44) may initiate trials of antiviral and antibacterial agents. Other approaches focusing on reparative and remyelinative strategies include efforts to block antibody-mediated demyelination. It may be possible to enhance remyelination by transplanting oligodendroglial precursorcells into discrete, clinically important lesions(e.g., those affecting the optic nerves, the middle cerebellar peduncle, or the spinal cord)(45,46) while administering growth factors and neuroprotective agents.

Gene-therapy strategies may also ultimately be worthy of study. Phase 3 studies should include at least three years of follow-up to identify biologically meaningful effects of treatment.(47,48).

ACUTE DISSEMINATED ENCEPHALOMYELITIS

Acute Disseminated encephalomyelitis *(ADEM)* is the *inflammatory demyelinating, immune mediated, monophasic, and polysymptomatic disorder* of the central nervous system white matter. It is usually followed by vaccination or viral infection. Multifocal symptoms involving various combinations of sensory, motor, gait, visual and memory disturbance or even as a psychiatric illness are seen. Most common age group affected is 1 year to 20 years. As it involves autoimmune demyelination, it is similar to multiple sclerosis, and is considered part of the Multiple sclerosis borderline[49,50]. The incidence rate is about 0.8 per 100,000 people per year[51]. . The mortality rate may be as high as 5%, full recovery is seen in 50 to 75% of cases, while up to 70 to 90% recover with some minor residual disability[52]. The average time to recover is one to six months.

ETIOLOGY:

A. <u>Post infectious encephalomyelitis</u>: Usually associated with viral exanthems - influenza virus ,measles, varicella, vaccinia, rubella, mumps, herpes, Epstein Barr virus, cytomegalovirus, hepatitis A, and coxsackievirus and in some cases bacteria like mycoplasma pneumoniae and legionella. Borrelia burgdorferi, Leptospira, and beta-hemolytic Streptococci(53)

B. <u>Post immunization encephalomyelitis</u>: The only vaccine proven to induce ADEM in the Semple form of the rabies vaccine, but hepatitis B, pertussis, diphtheria, measles, mumps, rubella, pneumococcus, varicella, influenza, Japanese encephalitis, and polio

vaccines have all been implicated[54-63].

C. <u>Post organ transplantation encephalomyelitis</u>: Long term immunosuppression leads to increased risk of acute infection, thus leading to ADEMS. Immunosuppressive agents such as methotrexate, cyclosporine, cyclophosphamide have been implicated in white

matter disease that resembles ADEMS.

PATHOPHYSIOLOGY:

It is predominantly a *white matter disease* with periventricular inflammation and demyelination. It is an *auto immune* response to central nervous system myelin.

CLINICAL FEATURES:

Abrupt onset of *multifocal neurological disorder* accompanied by generalized complaints of headache, fever, vomiting and mental state changes. The usual focal and multifocal signs reflect cerebral (hemiparesis, aphasia), brain stem (cranial nerve involvement) and spinal cord (paraparesis) involvement. . Recovery usually begins within few days with 50% cases having complete recovery. Mortality is around 30% in few studies. Features suggesting poor prognosis are hyperacute onset, coma and complicating seizures. Relapse is uncommon in cases with complete recovery.

DIAGNOSIS:

EEG - moderately to severe diffuse high voltage theta delta activity.

CSF - mild mononuclear pleocytosis, raised proteins, MBP content increased in 60%. Increased IgG index in < 10%.

MRI *Much more sensitive than CT Scan*. Early MRI facilitates diagnosis and can lead to early treatment with possible favorable outcome. T2 weighted MR images reveal multiple areas of increased signal intensity throughout the central nervous system that often correspond to the patient's clinical deficit. T2 weighted images are more sensitive than T1 weighted in detecting abnormalities. Contrast enhancement is usually seen. The lesions are usually symmetrical and involve subcortical white matter and deep seated grey matter including basal ganglia, thalamus and cerebellum. Rarely MRI appearance is that of ring enhancing lesion.

PROGNOSIS:

Full recovery is seen in 50 to 75% of cases, ranging to 70 to 90% recovery with some minor residual disability .Average time to recover is one to six months[52]. The mortality rate may be as high as 5%.[52]. Children tend to have more favorable outcomes than adults, and cases presenting without fevers tend to have poorer outcomes[64]. .

MOTOR DEFICITS:

Residual motor deficits are estimated to remain in about 8 to 30% of cases, the range in severity from mild clumsiness to ataxia and hemiparesis [53].

NEUROCOGNITIVE:

Patients with demylinating illnesses, such as MS, have been show cognitive deficits even when there is minimal physical disability[65]. Research suggests that similar effects are seen after ADEM, but that the deficits are less severe than those seen

in MS. A study of six children with ADEM (mean age at presentation 7.7 years) were tested for a range of neurocognitive tests after an average of 3.5 years of recovery. [66These deficits were less severe than those seen in similar aged children with a diagnosis of MS[67].

ADEM & MS:

While ADEM and MS both involve autoimmune demylenation, they differ in many clinical, genetic, imaging, and histopathological differences[68]. Some authors consider MS and its borderline forms to constitute a spectrum, differing only in chronocity, severity, and clinical course[69,70], while others consider them discretely different diseases[50].

TREATMENT:

A. Steroids Glucocorticoids and ACTH are treatment of choice. High dose corticosteroids (20 mg/kg as a single morning dose with or without maintenance therapy) are associated with a better chance of complete clinical recovery and prevention of relapse

B. Intravenous Immunoglobulin It has been beneficial when used early in the disease course as well as when used late after failure to respond to steroids. It has shown promising results in relapsing form of ADEMS.

C. Glatiramer acetate.

NEUROMYELITIS OPTICA

Neuromyelitis optica (NMO), or Devic's disease, is a monophasic syndrome consists of separate attacks of acute ON and myelitis occurring at the same time or in quick succession(71). ON may be unilateral or bilateral and precede or follow an attack of myelitis by days, months, or years. In contrast to MS, patients with NMO do not experience brainstem, cerebellar, and cognitive involvement, and the brain MRI is typically normal(72). A focal enhancing region of swelling and cavitation, extending over three or more spinal cord segments, is typically seen on MRI. Histopathology of these lesions may reveal thickening of blood-vessel walls and deposition of antibody .

A highly specific autoantibody directed against the water channel protein aquaporin-4 is present in the sera of more than half of patients who have a clinical diagnosis of NMO(73). Aquaporin-4 is localized to the foot processes of astrocytes in close apposition to endothelial surfaces. The role of aquaporin-4 antibodies in the pathogenesis of NMO, however, is unknown(74).

DIAGNOSTIC CRITERIA 2006 FOR NMO

Absolute Criteria

1.Optic neuritis

2.acute myelitis

Supportive criteria(at least 2-3)

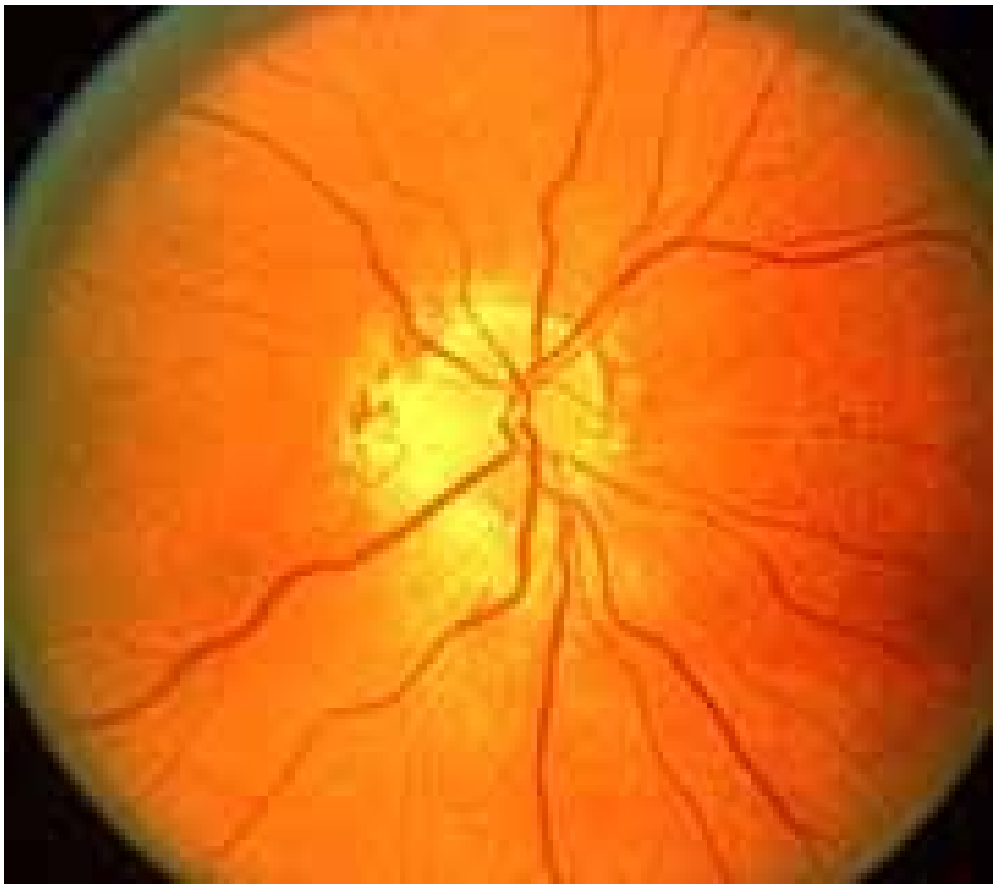
1.Negative brain MRI at onset.

2.spinal cord MRI with contigous T2weighted signal abnormality extending over 3 or more vertebral segments

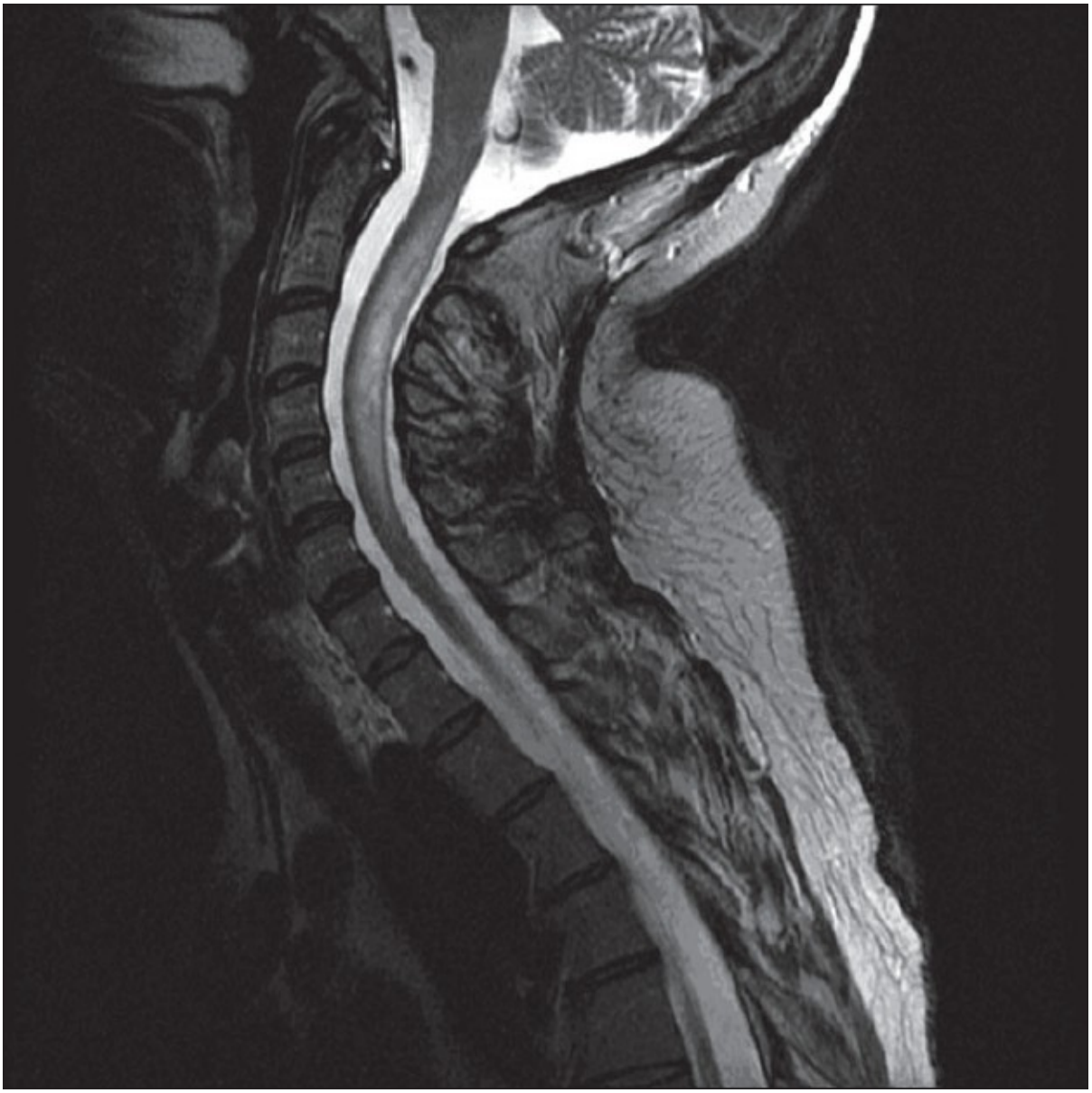
3.NMO Ig G seropositivity

OPTIC ATROPHY IN A PATIENT WITH DEVIC'S DIAEASE

Fig :10



39 year old woman who presented with acute myelitis. T2 weighted sagittal MRI of the cervical cord with longitudinally extensive spinal cord lesion. NMO Ig-G was positive Fig : 11



CEREBRO SPINAL FLUID:

During acute myelitis , prominent pleocytosis (with predominant polymorpho nuclear cells), of 50-1000 /microL. Oligoclonal bands Signifying intrathecal Ig synthesis are uncommon in NMO .

TREATMENT :

Disease-modifying therapies for MS have not been rigorously studied in NMO. **Acute attacks** are usually treated with high-dose glucocorticoids (1000 mg methyl predinosolone intravenously for 5 consecutive days)(75) as for MS exacerbations . Because of the possibility that NMO is antibody-mediated, plasma exchange has also been used empirically for acute episodes that fail to respond to glucocorticoids. Immunosuppressants (cyclophosphamide or azathioprine with glucocorticoids) are sometimes used in the hope that further relapses will be prevented. More recently, in a small open-case series, B cell depletion with anti-CD20 monoclonal antibody (rituxan) appeared to show promise in preventing relapses of NMO.

MATERIAL AND METHODS

STUDY DESIGN:

This is the prospective observational study conducted in coimbatore medical college hospital over the period of 18 months from April 2007 to September 2008. This study was approved by the ethics committee of our College.

STUDY POPULATION:

The study population involves Fifty suspected cases of demyelinating disease of central nervous system. The patients were selected from general medical ward and neuro medical ward.

INCLUSION CRITERIA:

Any male or female patients more than 13 years with long tract involvement (like pyramidal tract, MLF, posterior column, cerebellar pathways) with or without optic nerve and bladder involvement.

EXCLUSION CRITERIA:

Patients Without Evidence For Long Tract Involvement were excluded from this study.

SOURCE OF DATA:

Patients fulfilling the above criteria subjected to

1.Detailed history taking including history of recent respiratory tract infection, vaccination, fever ,viral exanthema,radiation and drug intake.

2.Detailed neurological examination.

3.Ophtholmological examination.

3.Informed written consent.

4..Routine blood and urine investigation;

urine analysis,complete hemogram,blood sugar,blood urea,serum creatinine and serum electrolytes.

5..ELISA for HIV

6.Antigen for Hepatitis B.

7..VDRL –Elisa for syphilis.

8. Vasculitis Profile :

- ANA
- DS-DNA,
- P-ANCA,
- C-ANCA,
- Antiphospholipid Antibody

. 9.CSF Analysis (pleocytosis,biochemistry,oligoclonal band)

10..MRI Brain and spine.

All the patients were treated with 1g IV methyl prednisolone for 5 days. Then put on oral prednisolone tapering dose and Azathioprine 2 mg/kg /d. All the patients were reassessed after 6 weeks. In cases of multiple sclerosis , the neurological deficit assessed with the help of KURTZKE -EDSS score and correlate the disability score with MRI findings.

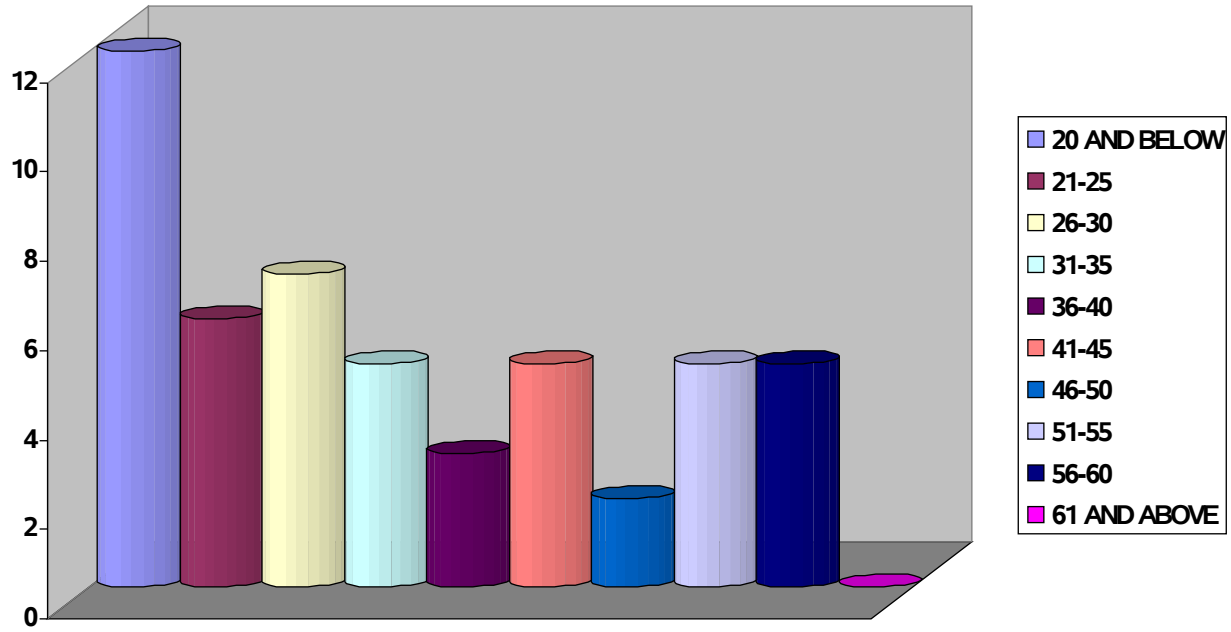
OBSERVATION AND ANALYSIS

AGE DISTRIBUTION:

The age distribution among 50 patients showed that , demyelinating diseases of CNS were common in younger age group below 30 years.

(Table : 4)

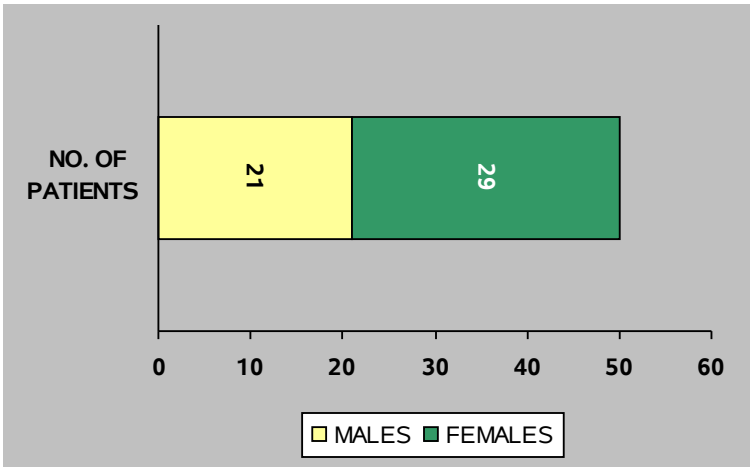
AGE IN YEARS	NO. OF PATIENTS
20 AND BELOW	12
21-25	6
26-30	7
31-35	5
36-40	3
41-45	5
46-50	2
51-55	5
56-60	5
61 AND ABOVE	0



GENDER DISTRIBUTION:

It was oberved that the frequency of occurrence of demyelinating disorders was higher among females than males (Table : 5)

GENDER	NO. OF PATIENTS
MALES	21
FEMALES	29



CLINICAL PRESENTATION:

Clinically most of the patients presented with weakness in the form of paraparesis, paraplegia,quadriplegia,quadriparesis, weakness of both upper limbs, monoperesis and hemiparesis. Four patients presented with Sensory involvement in the form of numbness and paraesthesia. Reduced vision with the fundus examination showing optic atrophy in two patients. Three patients presented with bilateral internuclear ophtholmoplegia indicating the involvement of medial longitudinal fasciculus . One patient presented with cerebellar ataxia. Ten patients presented with symptoms suggestive of bladder involvement.

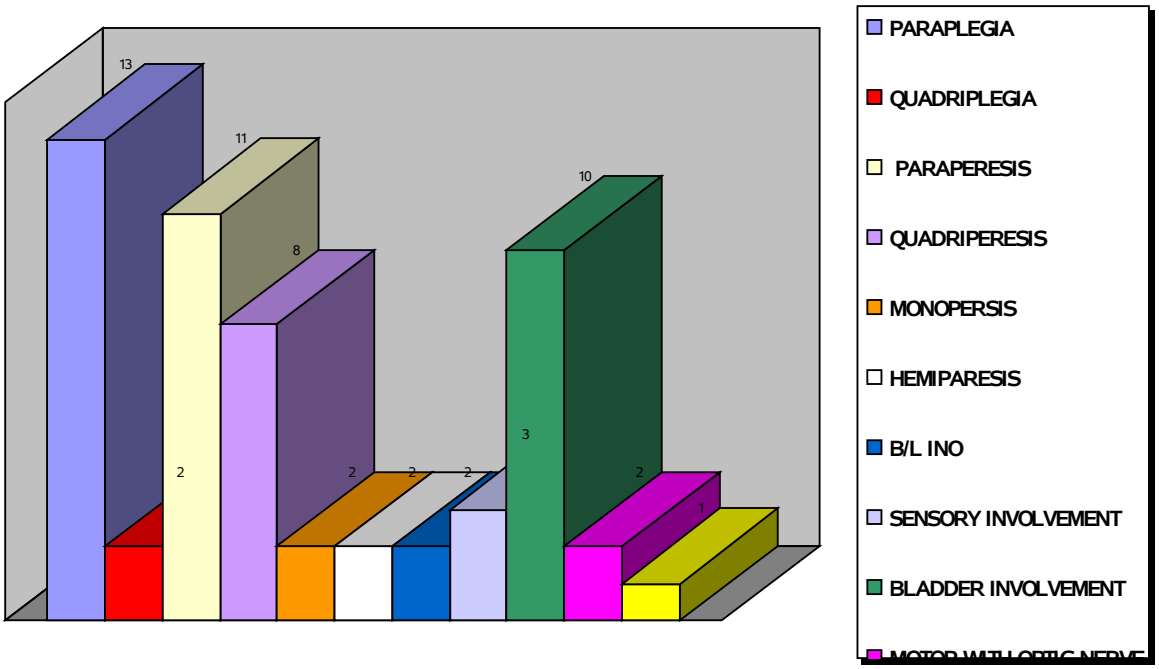
Fifteen patients gave past history of acute febrile illness, respiratory tract

infection,herpes zoster and chicken pox prior to the onset of neurological illness.

Twelve patients gave history of similar illness in the past.

(Table : 6)

CLINICAL PRESENTATION	NO. OF CASES
PARAPLEGIA	13
QUADRIPLEGIA	2
PARAPERESIS	11
QUADRIPERESIS	8
MONOPERSIS	2
HEMIPARESIS	2
B/L INO	2
SENSORY INVOLVEMENT	3
BLADDER INVOLVEMENT	10
MOTOR WITH OPTIC NERVE INVOLVEMENT	2
ATAXIA& SENSORY	1



INVESTIGATIONS:

Apart from the routine blood investigations, specific investigations to find out the secondary cause of demyelination include HIV Elisa, VDRL, and HBs Ag were done for all the cases. Two casse were positive for HIV ELISA test. All the patients were negative for VDRL, and HBs Ag.

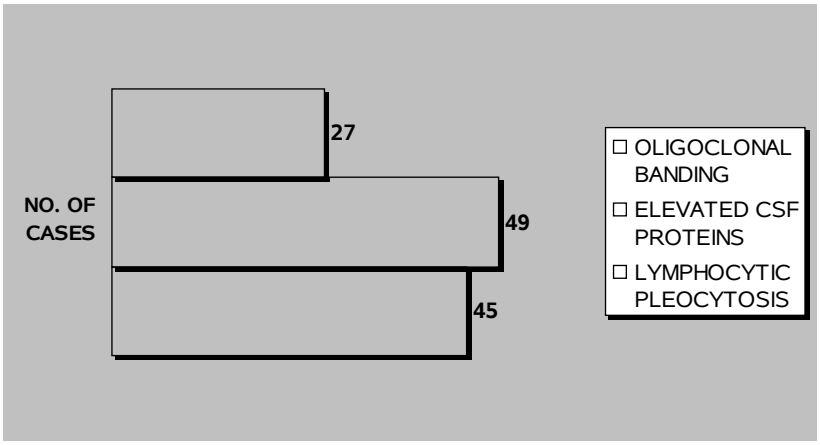
CSF ANALYSIS:

The major abnormalities looked for in the CSF analysis include the cell count which showed lymphocytic pleocytosis in 90% of the patients. CSF proteins were elevated in 49 patients of demyelinating diseases.

Oligoclonal banding was positive in 27 (54%) of the patients and negative for the remaining cases.

(Table : 7)

CSF FINDINGS	NO. OF CASES
LYMPHOCYTIC PLEOCYTOSIS	45
ELEVATED CSF PROTEINS	49
OLIGOCLONAL BANDING	27



MRI BRAIN AND SPINE:

The T2 weighted MRI images show the Hyperintense lesions in the following sites.

1. Spinal cord
2. Periventricular white matter
3. Pontine tegmentum
4. Mid brain
5. Medial longitudinal fasciculus
6. Corpus callosum
7. Corona radiata
8. Cerebellum
9. Middle cerebellar peduncle
10. Conus
11. Peri aque-duct
12. Parietal lobe and
13. optic nerve

The spinal cord lesions are commonly seen in cervical and dorsal cord. The lesions may be either diffuse or patchy and include demylinating plaques and cord edema.

In MRI Imaging studies, the regional distribution of the various

sites of involvement of demyelination is as follows.

In spinal cord, cervical region – 7 cases

Dorsal region – 17 cases

Cervico-dorsal – 17cases

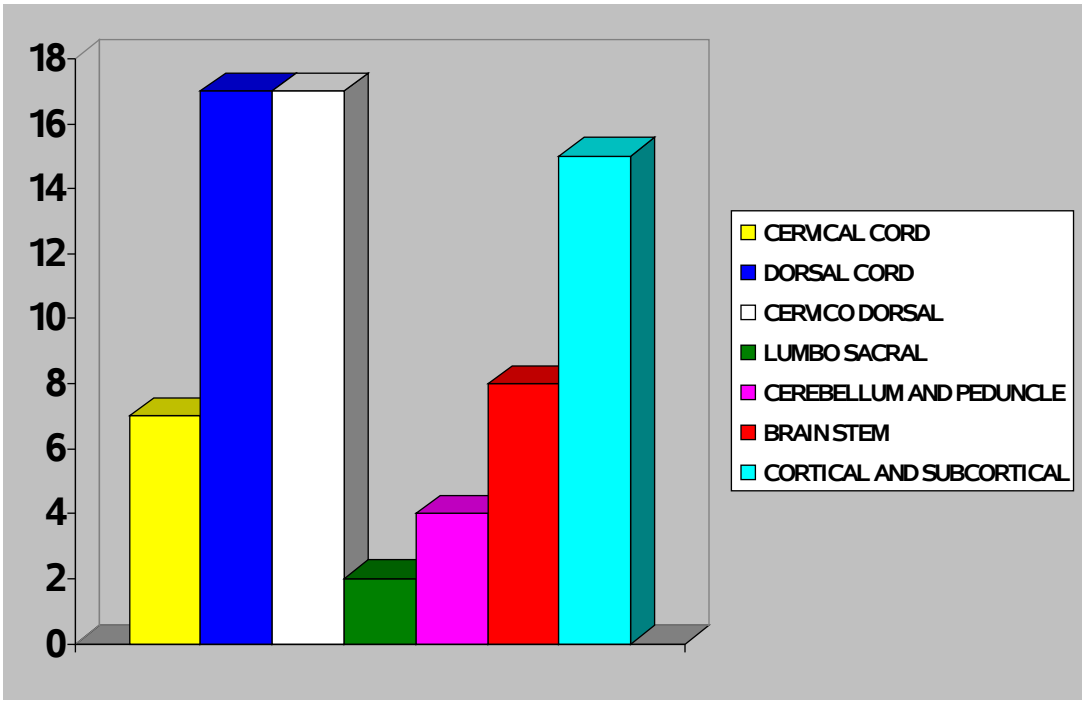
Lumbo-sacral – 2 cases

Cerebellum and peduncle – 4 cases.

Brain stem – 8 cases.

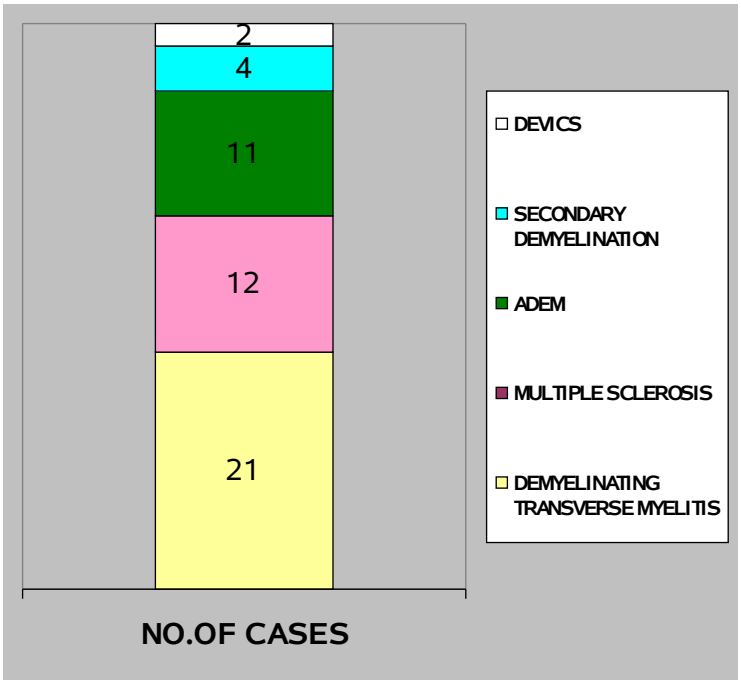
Cortical and subcortical regions including periventricular white matter, corpus callosum, coronaradiata&parietal cortex – 15 cases (Table : 8)

SITE OF INVOLVEMENT	**NO.OF CASES**
CERVICAL CORD	7
DORSAL CORD	17
CERVICO DORSAL	17
LUMBO SACRAL	2
CEREBELLUM AND PEDUNCLE	4
BRAIN STEM	8
CORTICAL AND SUBCORTICAL	15



FREQUENCY OF DEMYELINATING DISORDERS (Table : 9)

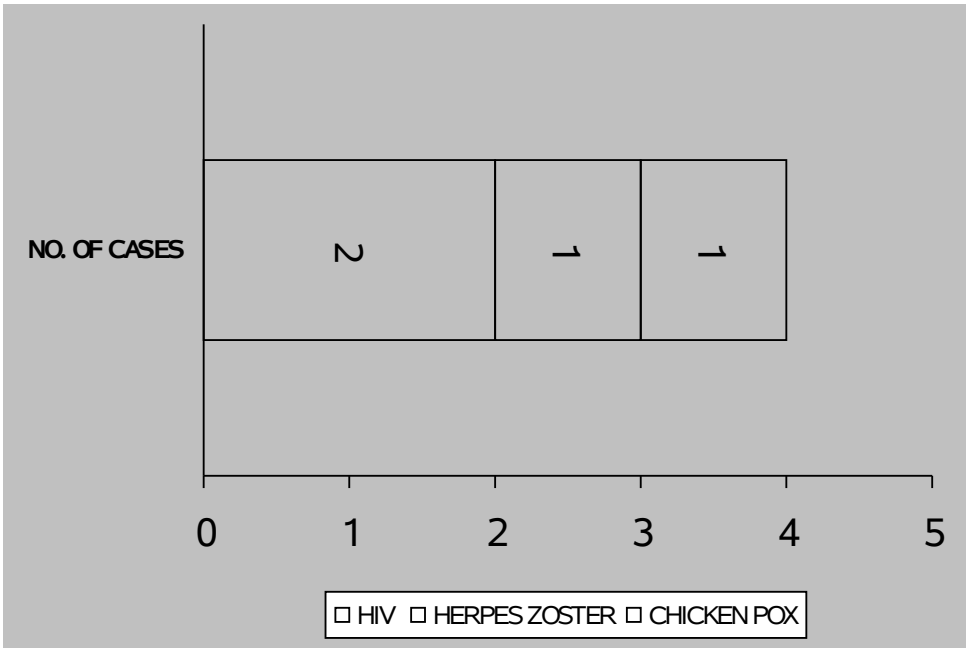
DIAGNOSIS	NO.OF CASES
DEMYELINATING TRANSVERSE MYELITIS	21
MULTIPLE SCLEROSIS	12
ADEM	11
SECONDARY DEMYELINATION	4
DEVICS	2



SECONDARY DEMYELINATION:

The secondary cause for demyelination was found in 4 cases of ADEM (Table : 10)

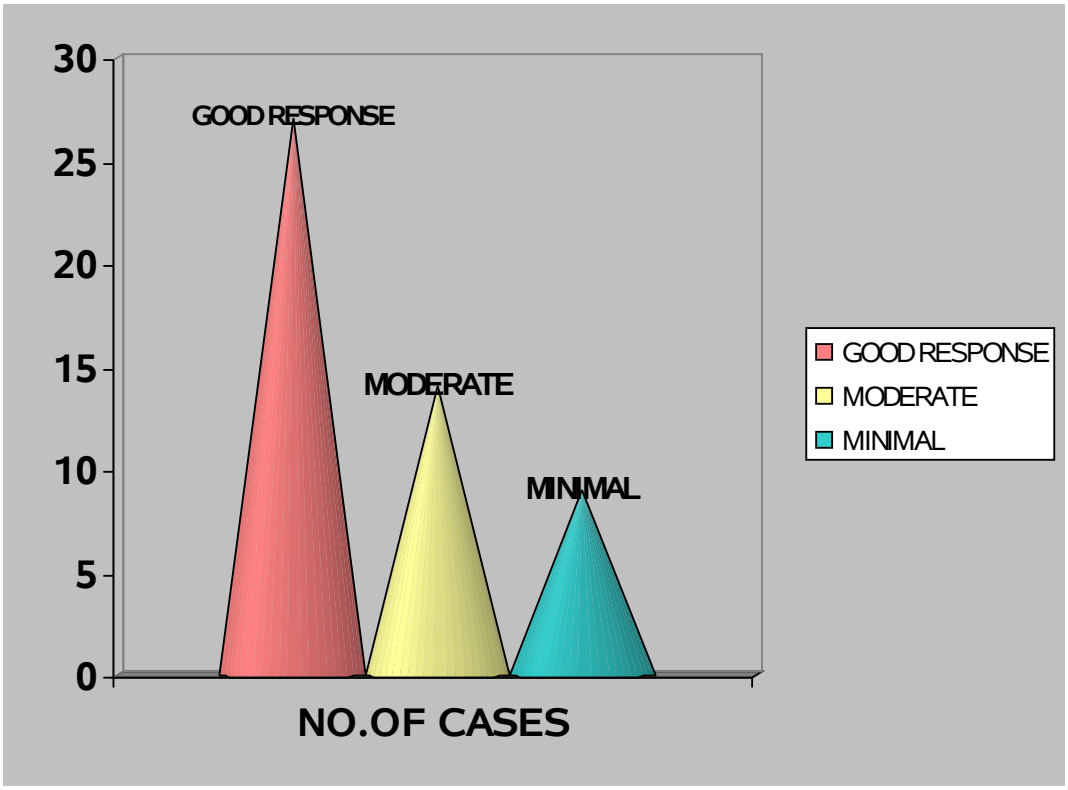
SECONDARY DEMYELINATION	NO. OF CASES
HIV	2
HERPES ZOSTER	1
CHICKEN POX	1



RESPONSE TO PULSE STEROID THERAPY:

All the patients of this study were treated with pulse steroid regimen, INJ.METHYL PREDNISLONE 1G Daily for 5 days. (Table : 11)

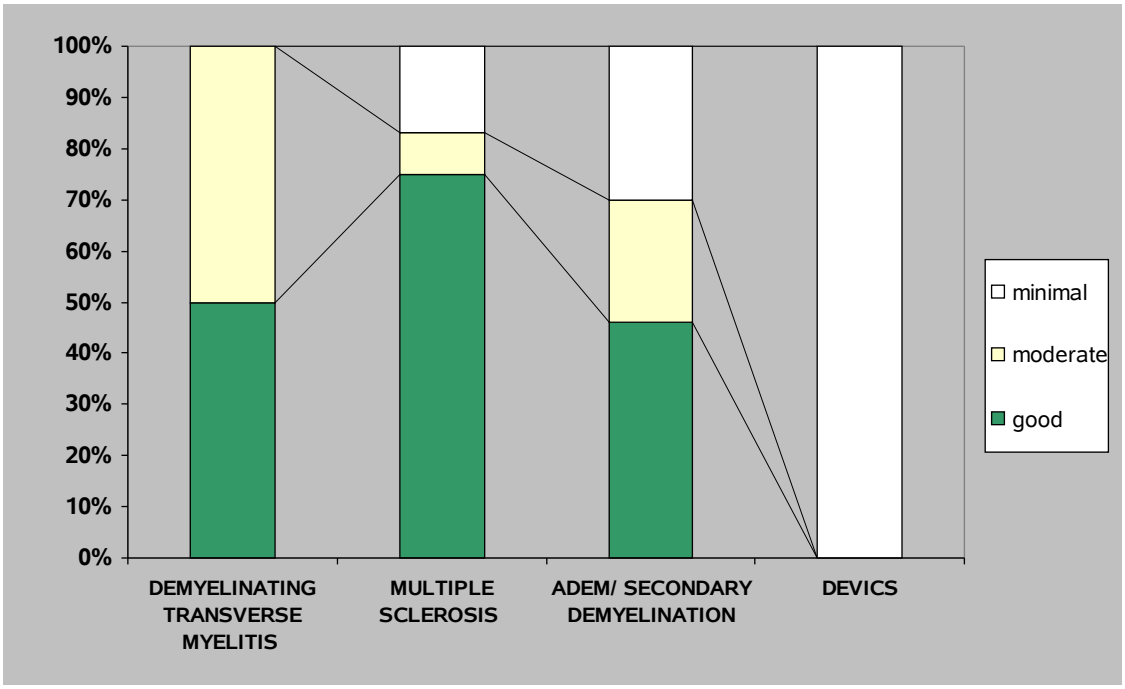
RESPONSE TO STEROIDS	**NO.OF CASES**
GOOD RESPONSE	27
MODERATE	14
MINIMAL	9



RESPONSE IN VARIOUS DEMYELINATING DISEASES:

(Table : 12)

DIAGNOSIS	GOOD %	MODERATE%	MINIMAL%
DEMYELINATING TRANSVERSE MYELITIS	50	50	--
MULTIPLE SCLEROSIS	75	8	17
ADEM/ SECONDARY DEMYELINATION	46	24	30
DEVICS	--	--	100


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
DEMYELINATING TRANSVERSE MYELITIS
MULTIPLE SCLEROSIS
ADEM/ SECONDARY DEMYELINATION
DEVICS
minimal
moderate
good

DISCUSSION

AGE DISTRIBUTION :

In this study, the age distribution in demyelinating disorders of the central nervous system showed that younger age groups were more affected , 50% of the patients belong to less than 30 years of age.

SEX PREDILECTION :

With regards to the sex predilection, females were more affected(58%), than males(42%).

CLINICAL PRESENTATION :

The clinical presentation varied from motor weakness in the form of paraplegia, paraperesis, quadriplegia, quadriparesis, monoperesis, or rarely hemiplegia, sensorvolvement in the form of paraesthesia, brain stem involvement in form of bilateral INO , optic nerve involvement with optic atrophy, cerebellar ataxia, and bladder involvement. Two patients presented with optic atrophy and paraplegia. Two patients presented with bilateral INO with past history of similar illness.

CSF ANALYSIS :

In this study, 90% of the patients showed **lymphocytic pleocytosis** in CSF analysis.49 patients of this study showed elevated CSF protiens.

The measure of **oligoclonal band** in CSF is to assess the intrathecal

production of Ig G. About 75% of multiple sclerosis patients usually show positive oligo clonal band in CSF studies. But in this study only 54% of patients showed positive oligoclonal band in CSF. The presence of oligoclonal bands in cerebrospinal fluid slightly increases the risk of recurrent disease.(32)

MRI IMAGING:

In MRI Imaging studies, the regional distribution of the various sites of involvement of demyelination is as follows.

In spinal cord, cervical region – 7 cases

Dorsal region – 17 cases

Cervico-dorsal – 17cases

Lumbo-sacral – 2 cases

Cerebellum and peduncle – 4 cases.

Brain stem – 8 cases.

Cortical and subcortical regions including periventricular white matter, corpus callosum, coronaradiata&parietal cortex – 15 cases.

Vasculitic profile was done only in 4 patients randomly among which one patient is positive for ANA and one patient is positive for P-ANCA.

DIAGNOSIS:

In this study,

Twelve patients were diagnosed to have multiple sclerosis,

Two patients were diagnosed to have DEVIC'S disease,

Eleven patients were diagnosed to have ADEM.

Four patients were diagnosed to have Secondary Demyelination, among which two cases were HIV ELISA positive, one case occurred following Herpes Zoster, one case occurred following chicken pox.

Twenty one cases were diagnosed to have clinically isolated syndrome of demyelination presented in the form of idiopathic demyelinating transverse myelitis .These patients had 70-80% chance of devoleping multiple sclerosis later as the MRI images of these cases showed more than three T2 weighted lesions in spinal cord. (31)

Hence these patients need further regular follow up with MRI imaging studies.

DISABILITY SCORE :

The disability score in MS is calculated with **KURTZKE'S** Expanded Disability Status Score (**EDSS) Scoring system.**

One patient had EDSS score of 2.0

Six patients had EDSS score between 3- 3.5

Two patients had EDSS score between 4-4.5

Three patients had EDSS score of 6.0

Patients with periventricular T2 weighted lesions and posterior fossa lesions

in MRI had more disability with EDSS score of 6.0

So the MRI imaging studies provide more prognostic information than clinical assessment.

RESPONSE TO STEROID THERAPY :

All the patients were treated with 1g IV methyl prednisolone for 5 days. Then put on oral prednisolone tapeing dose and Azathioprine 2mg/kg/d. All the patients were reassessed after 6 weeks. 54% of the patients showed good response. 28% of the patients showed moderate response and 18% of the patients showed minimal response.

The **response to steroid therapy** was good in 75% of MS patients , 50% of the idiopathic demyelinating transverse myelitis patients and in 46% of the ADEM cases.

FOLLOW UP:

All the patients were followed up for six weeks after steroid therapy. The recovery form neurological impairment was good in 75% of MS patients , 50% of the idiopathic demyelinating transverse myelitis patients and in 46% of the ADEM cases. In Devics disease there was only minimal improvement in visual function. This is because of their late presentation to the hospital.

Patients who had more than three segmental involvement in spinal cord and those with more than three peri callosal, peri ventricular and posterior fossa lesions in MRI images showed poor clinical recovery.

SUMMARY

Demyelinating disorders of the central nervous system were common among younger age group patients(50%).Females were more affected than males. (58% vs 42%).

Most of the patients presented with pyramidal tract involve ment-68%. Bladder involvement seen in 20% of patients and the remaining cases presented with brain stem , cerebellar ,optic nerve and sensory involvement. Four patients had Secondary Demyelination, among which two cases were HIV ELISA positive, one case occurred following Herpes Zoster, one case occurred following chicken pox.

CSF analysis showed positive oligoclonal band in 54% of the patients.

Patients with periventricular T2 weighted lesions and posterior fossa lesions in MRI had more disability with EDSS score of 6.0

Primary demyelinating diseases were more common than secondary demyelinating diseases. Primary demyelinating disorders include twelve cases of Multiple Sclerosis, two cases of Devic's disease and eleven cases of ADEM.

There were four cases of Secondary demyelinating disorders, the causes of which include HIV in 2 patients, Herpes Zoster in one patient and Chicken pox in one patient.

Twenty one cases were diagnosed to have clinically isolated syndrome of demyelination presented in the form of idiopathic demyelinating transverse myelitis. These patients had 70-80% chance of devoleping multiple sclerosis later as the MRI

images of these cases showed more than three T2 weighted lesions in spinal cord. Hence these patients need further regular follow up with MRI imaging studies.

The response to steroid therapy was good in 75% of MS patients , 50% of the idiopathic demyelinating transverse myelitis patients and in 46% of the ADEM cases. All the patients were followed up for six weeks after steroid therapy Patients who had more than three segmental involvement in spinal cord and those with more than three peri callosal, peri ventricular and posterior fossa lesions in MRI images showed poor clinical recovery

CONCLUSION

1. **Demyelinating disorders of the central nervous system are common among younger age group patients**

2. **Females are more affected than males.**

3. **Primary demyelinating diseases are more common than secondary demyelinating diseases.**

4. **Clinically isolated demyelination syndrome patients need regular follow up with MRI imaging in due course.**

5. **Patients with more than three segmental involvement in spinal cord and those with more than three peri-callosal, peri- ventricular and posterior fossa lesions in MRI images has poor clinical recovery after treatment.**

6. **MRI brain and spine provides more prognostic information than clinical assessment.**

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ANNEXURE

PROFORMA

NAME :

AGE : GENDER :

OCCUPATION : IP.NO :

DIAGNOSIS :

COMPLAINTS : WEAKNESS/ATAXIA/DIPLOPIA/NUMBNESS

H/O PRESENT ILLNESS :

- WEAKNESS, NUMBNESS
- MODE OF ONSET,PROGRESSION
- UNSTEADINESS
- NECKPAIN/BACK PAIN (LHERMITTE SIGN)
- UTHOFF'S PHENOMENON
- BLADDER INVOLVEMENT
- VIRAL EXANTHEM,FEVER, VACCINATION,
- RESPIATORY INFECTION,
- RADIATION AND DRUG INTAKE

PAST HISTORY : SIMILAR ILLNESS IN THE PAST
RECURRENCE/RELAPSE

PERSONAL HISTORY :SMOKING/ALCOHOL/EXPOSURE TO STD

FAMILY HISTORY :

TREATMENT HISTORY :

GENERAL EXAMINATION:

CNS EXAMINATION

HIGHER FUNCTIONS :

CRANIAL NERVES INCLUDING FUNDUS:

- SPINOMOTOR SYSTEM
- BULK
- TONE
- POWER

- REFLEXES
- COORDINATION
- INVOLUNTARY MOVEMENTS
- GAIT

SENSORY SYSTEM:

SPINOTHALAMIC SENSATIONS:

-PAIN,TOUCH&TEMPARATURE

POSTERIOR COLUMN SENSATIONS:

-VIBRATION AND JOINT POSITION SENSE

AUTONOMIC NERVOUS SYSTEM :

EXTRAPYRAMIDAL SYSTEM :

SPINE AND CRANIUM :

MENINGEAL SIGNS :

EXAMINATION OF OTHER SYSTEMS

- CARDIOVASCULAR SYSTEM
- RESPIRATORY SYSTEM
- GASTRO INTESTINAL SYSTEM

PROVISIONAL DIAGNOSIS:

EDDS SCORE FOR MULTIPLE SCLEROSIS PATIENTS:

INVESTIGATIONS:

COMPLETE BLOOD COUNT :

BLOOD SUGAR :

BLOOD UREA :

SERUM CREATINIE :

HIV ELISA :

VDRL ELISA :

VIRAL MARKERS FOR HEPATITIS:

CSF ANALYSIS :

CYTOLOGY

PROTEINS

OLIGICLONAL BANDS

MRI – BRAIN AND SPINE :

NERVE CONDUTION STUDY :

VASCULITIS PROFILE :

- ANA
- DS-DNA,
- P-ANCA,
- C-ANCA,
- ANTIPHOSPHOLIPID ANTIBODY